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Seasonal variation in frequency of diagnosis of cutaneous malignant melanoma

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Incident cases of *in situ* and invasive cutaneous malignant melanoma diagnosed during 1975–90 were identified through the National Cancer Institute's Surveillance, Epidemiology, and End Results program. We studied the 32 868 white subjects diagnosed with melanoma, who were living in nine cancer registry areas covering approximately 10% of the population of the USA. The summer-to-winter ratio, defined as the ratio of the number of melanomas diagnosed during June to August (summer), to the number of melanomas diagnosed during December to February (winter), was determined according to gender, stage, histologic type and anatomic site. Summer-to-winter ratios were 1.47 (95% confidence interval (CI) 1.37–1.58) for *in situ*; 1.43 (95% CI 1.38–1.48) for local stage; 1.24 (95% CI 1.12–1.38) for regional stage; and 0.95 (95% CI 0.82–1.11) for distant stage melanoma. For the melanomas staged as local at diagnosis (86% of the invasive melanomas staged), a July peak was observed. For each of the major histological types of local stage melanoma, summer-to-winter ratios were significantly elevated in men (range 1.24–1.41) and women (range 1.44–1.90). For the major anatomic sites (including the head and neck, which are exposed throughout the year) of local stage melanoma, summer-to-winter ratios were elevated for men (range 1.28–1.45) and for women (range 1.31–1.75). Although some of the seasonal variation in frequency of diagnosis of cutaneous melanoma may be due to a greater likelihood of detection during the summer months, when less clothing is worn and more skin is visible, we conclude that the seasonal variation is due at least in part to relatively recent exposure to sun. These findings may hold clues to the last stages of carcinogenesis, and suggest that avoiding excessive exposure to the sun may decrease the risk of melanoma in the short term as well as the long term.

Key words: Aetiology, diagnosis, epidemiology, melanoma, seasons, sunlight.

Introduction

The aetiologic importance of heavy exposure to sun light in childhood for cutaneous malignant melanoma is generally recognized.[1] However, the effect on melanoma risk of solar exposure that occurs closer in time to the diagnosis of melanoma is less clear.

Data have been reported recently that are consistent with the hypothesis that decreasing recent exposure to sun light may decrease the incidence of and mortality from cutaneous malignant melanoma (although other explanations of the data are also possible). Indications of declining trends in melanoma incidence and mortality have been reported for the youngest generations and linked to relatively recent improvements in habits of exposure to sun light and earlier detection of melanoma.[2,3] In addition, an increase from youth to old age in the influence of latitude on melanoma incidence and mortality has been reported, suggesting that exposures close in time to the incidence of melanoma play a significant aetiologic role.[4] Further, melanoma incidence decreased among a group of high-risk members of melanoma-prone families approximately 5 years after enrolling in a prospective study and being counselled to reduce their exposure to the sun.[5]

The frequency of diagnosis of cutaneous malignant melanoma has been found in several studies to be seasonal, with a peak in summer and a trough in winter, leading to suggestions that exposure to the sun may be a short-term promoter of melanoma.[6-10] However, clear appreciation of the seasonality of melanoma and its implications has been hindered by varying results in subgroup analyses according to gender, histologic type and anatomic site. These varying findings probably resulted at least in part from study sample sizes that provided insufficient statistical power.

Using data from the Surveillance, Epidemiology, and End Results (SEER) program,[11] we have analysed two-and-a-half times the number of invasive melanoma cases of the largest previous study, also based on SEER data.[8] We also present new analyses of the seasonality of melanoma diagnosis, taking into account the stage of disease at diagnosis and tumour thickness. In addition, we had the opportunity to evaluate the seasonal patterns among a cohort of individuals from melanoma-prone families that are under prospective surveillance.

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Subjects and methods

Individuals diagnosed as having cutaneous malignant melanoma were ascertained through the nine population-based cancer registries that compose the National Cancer Institute SEER program.[11] These state and metropolitan area registries include approximately 10% of the US population. States included are Connecticut, Hawaii, Iowa, New Mexico and Utah. Metropolitan areas included are San Francisco/Oakland, CA; Detroit, MI; Seattle, WA; and Atlanta, GA.

All cutaneous malignant melanomas, classified according to the International Classification of Diseases for Oncology (ICDO)[12] morphology codes M-8720–M-8779 reported among residents during 1975–90 were analysed in this study. Cutaneous malignant melanomas were classified into the following histologic categories: superficial spreading (ICDO code M-8743); nodular (ICDO code M-8721); lentigo maligna (ICDO code M-8742); and 'not otherwise specified' (ICDO code M-8720). These histologic types represent 97% of the invasive and *in situ* cutaneous malignant melanomas reported. Because of small numbers, 11 other histologic types of cutaneous malignant melanoma were not analysed individually, although these types are included in aggregate analyses. Eleven cases of blue nevi (ICDO codes M-8780, M-8790) were excluded from all analyses.

Cutaneous malignant melanoma is relatively rare in black individuals, who composed 0.6% of the total number of cases, providing insufficient numbers for the analyses performed. Therefore, the analysis was restricted to white subjects. Similarly, persons of other or unknown race, composing 5.5% of all cases, were also excluded from the analysis.

The cutaneous melanomas were also classified by stage at diagnosis: *in situ*; localized; regional; or distant.[13] Local cutaneous malignant melanomas were grouped by anatomic site: head and neck (ICDO codes T-173.0–T-173.4); arm and shoulder (ICDO code T-173.6); trunk (ICDO code T-173.5); and leg and hip (ICDO code T-173.7). These four anatomic sites compose 97% of the local cutaneous malignant melanomas reported in white subjects. Other less commonly affected sites and sites not otherwise specified were not analysed individually, but are included in aggregate analyses.

The two graphs of seasonal variation in date of diagnosis of melanoma reported to the SEER program are both presented in a semi-log format, using the same abscissae and ordinates. In contrast to graphs using an arithmetic ordinate, this semi-log format using the same axes in both graphs allows visual comparison of proportional changes among all groups.

The 95% confidence intervals (CIs) of ratios of the number of cases of cutaneous malignant melanoma diagnosed during the warmest months (June, July and August; referred to here as summer) to the number of cases diagnosed during the coldest months (December, January and February; referred to here as winter) were computed by a log-linear model. The p values obtained from the analyses using only the summer and winter months in the log-linear model were nearly identical to the p values obtained from analyses using all 12 months in Edwards' test for recognition and estimation of cyclic trends.[11] For simplicity of presentation, only the analyses using the summer and winter months are reported here. We also fit a multivariate Poisson regression model to our data, using a modified version of the GLIM computer program, version 3.77. This model showed that among local stage cutaneous malignant melanomas, adjustment for age, gender, calendar year, histologic type, and anatomic site had virtually no effect on the results; therefore, results of univariate analyses are presented.

Seasonality of diagnosis was also investigated for cancers of the lung, breast, colon, rectum, stomach, prostate, testis, ovary, cervix and pancreas. In contrast to cutaneous malignant melanoma, no clear seasonal patterns were observed for these other common cancers.

Prospectively identified cutaneous malignant melanomas in high-risk individuals

A cohort study of 364 members of 23 melanoma-prone families has recently been described in detail elsewhere.[5] (This study is unrelated to the National Cancer Institute SEER program.)

Members of the cohort have been counselled about their high risk for melanoma and instructed to perform skin self-examination at least monthly. In addition, they undergo a skin examination by a physician two to four times each year. To evaluate seasonality of diagnosis of cutaneous malignant melanoma among persons participating in such a program of active surveillance for melanoma, we analysed the month of diagnosis of each newly incident melanoma in the study cohort. Prevalent melanomas that were diagnosed at the time of entry into the study are neither described nor analysed here.

Results

During 1975–90, there were 32 868 invasive cutaneous malignant melanomas diagnosed among white subjects (52% of the cases were men and 48% were women) in the SEER program areas. Superficial spreading melanoma accounted for 40% of the cutaneous malignant melanomas; nodular, 11%, lentigo, 6%; and in 40% the histology was not specified. All these types showed a seasonal pattern with a July peak—except that lentigo, the rarest type, peaked in May (Figure 1). Table 1 shows that, depending on histologic type, the number of cutaneous malignant melanoma cases diagnosed in summer exceeded the number diagnosed in winter by 27–54%.

Of the 30 160 invasive cutaneous malignant melanomas staged at diagnosis, 25 956 (86%) were staged as local; 2878 (10%) had spread to regional sites; and 1326 (4%) had distant metastases. There were also 6366 reported cases of *in situ* disease. Melanoma cases staged as *in situ* or local at diagnosis showed a clearly seasonal trend with a July peak (Figure 2); summer cases exceeded winter cases by 47% and 43%, respectively (Table 1). Although cutaneous malignant melanoma cases staged as regional were much less common, they also showed a seasonal trend, with an April peak; summer cases exceeded winter cases by 24%. Melanoma with distant metastases showed no clear seasonal pattern; there were 5% fewer summer cases than winter cases. In addition, data on tumour thickness were available for 1988–90. Within the category of melanomas staged as local at diagnosis, a pattern of decreasing seasonality with more advanced disease was also observed: the ratio of summer cases to winter cases decreased from 1.63 for tumours of ≤ 0.75 mm thickness to 1.43 for

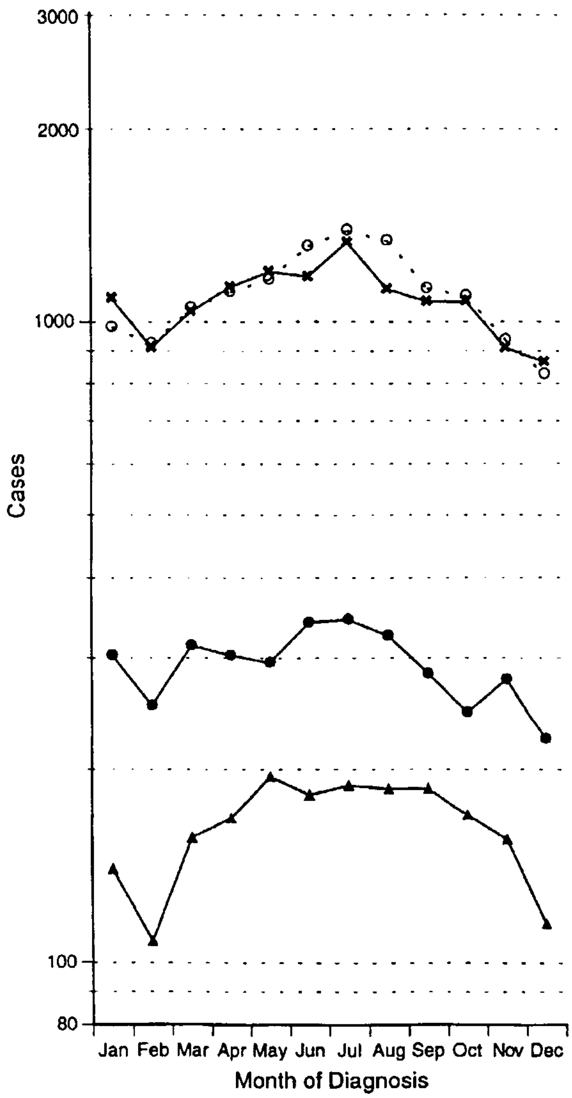

Figure 1. Invasive cutaneous malignant melanoma among white subjects, by histologic type and month of diagnosis. Data from the NCI Surveillance, Epidemiology, and End Results program (SEER) 1975–90. O, Superficial spreading; ●, nodular; ▲, lentigo; and ✖, not specified.

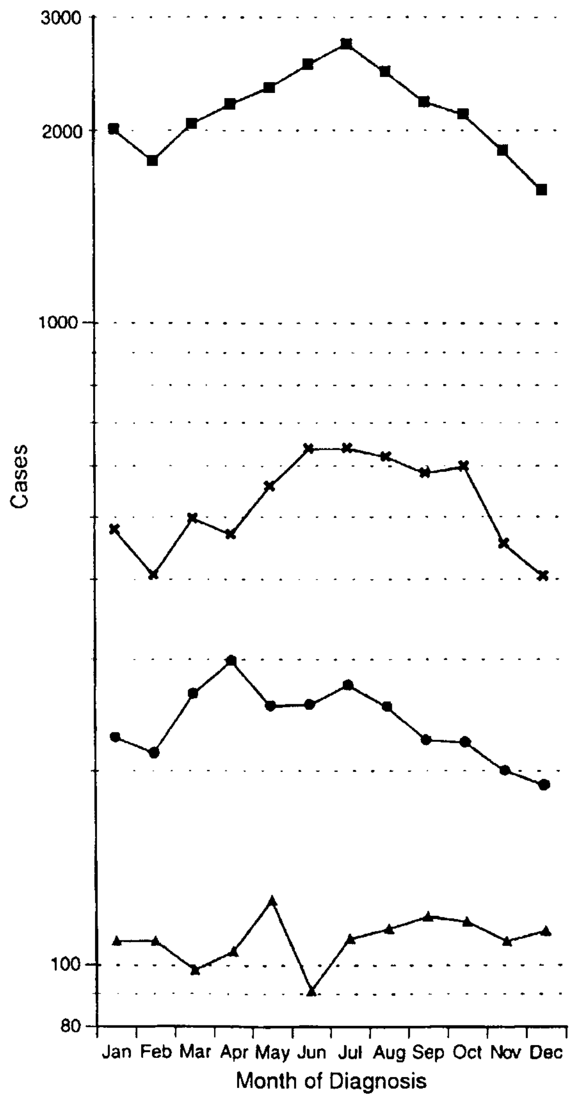

Figure 2. Cutaneous malignant melanoma among white subjects, by month and stage at diagnosis. Data from the NCI Surveillance, Epidemiology, and End Results program (SEER) 1975–90. ✖, *In situ*; ■, local; ●, regional; and ▲, distant.

Table 1. Seasonality of cutaneous malignant melanoma: a comparison of the number of cases reported in summer with those in winter (data from SEER program, 1975–90).

	Summer cases (*n*)	Winter cases (*n*)	Ratio (95% confidence intervals)
Histologic type[a]			
Superficial spreading	4043	2732	1.48 (1.41–1.55)
Nodular	1011	779	1.30 (1.18–1.42)
Lentigo	559	363	1.54 (1.35–1.76)
Not specified	3629	2862	1.27 (1.21–1.33)
Stage at diagnosis			
In situ	1893	1287	1.47 (1.37–1.58)
Local	7718	5412	1.43 (1.38–1.48)
Regional	781	628	1.24 (1.12–1.38)
Distant	315	331	0.95 (0.82–1.11)
Tumour thickness (local stage only) (mm)[b]			
≤ 0.75	945	580	1.63 (1.46–1.81)
0.76–1.5	350	233	1.50 (1.26–1.77)
> 1.5	244	171	1.43 (1.17–1.74)

[a]Invasive melanomas only.
[b]Reported for 1988–90 only.

tumours > 1.5 mm, although this trend did not achieve statistical significance (Table 1).

Cutaneous malignant melanoma staged as local at diagnosis showed highly statistically significant summer excesses among men and women, with smaller summer excesses among men than among women. Summer cases exceeded winter cases by 32% among men (range 24–41%, depending on histologic type) and by 55% among women (range 44–90%, depending on histologic type) (Table 2).

The four major anatomic regions, head and neck, arm and shoulder, trunk, and leg and hip, all showed highly statistically significant summer excesses of local stage cutaneous malignant melanoma (Table 3). The summer excesses among women exceeded those among men significantly for two anatomic sites: arm and shoulder (75% among women compared with 45% among men), and leg and hip (65% among women compared with 30% among men). The gender differences in the ratios were not removed in analyses that controlled for stage of disease and tumour thickness (data not shown).

Prospectively identified cutaneous malignant melanomas in high-risk individuals

Forty-nine cutaneous malignant melanomas were prospectively diagnosed in 24 members of melanoma-prone families, subsequent to their initial screening. Figure 3 shows the frequency distribution of the month of diagnosis of these melanomas. Although the number of cases is small, the seasonal pattern of melanoma diagnosis resembles that of the SEER program data.

Discussion

Our findings demonstrate for the first time that the frequency of diagnosis of local stage cutaneous malignant melanoma is seasonal for men and women, for all major histologic types, and for all major body sites. Is this seasonality of melanoma diagnosis occurring because of a biological process, or rather simply because of a greater

Table 2. Seasonality of cutaneous malignant melanoma, staged as local at diagnosis: number of cases reported in summer compared with those reported in winter (data from SEER program, 1975–90).

	Summer cases (*n*)	Winter cases (*n*)	Ratio (95% confidence intervals)
Histologic type: men			
Superficial spreading	1724	1263	1.37 (1.27–1.47)
Nodular	384	310	1.24 (1.07–1.44)
Lentigo	274	195	1.41 (1.18–1.69)
Not specified	1320	1035	1.28 (1.18–1.38)
Histologic type: women			
Superficial spreading	2038	1274	1.60 (1.49–1.72)
Nodular	348	223	1.56 (1.32–1.85)
Lentigo	224	118	1.90 (1.52–2.38)
Not specified	1263	877	1.44 (1.32–1.57)

Table 3. Seasonality of cutaneous malignant melanoma, staged as local at diagnosis, by anatomic region: number of cases reported in summer compared with those reported in winter (data from SEER program, 1975–90).

	Summer cases (*n*)		Winter cases (*n*)		Ratio (95% confidence intervals)	
	Men	Women	Men	Women	Men	Women
Head and neck	806	488	632	345	1.28 (1.15–1.42)	1.41 (1.23–1.62)
Arm and shoulder	842	1091	580	624	1.45 (1.31–1.61)	1.75 (1.58–1.93)
Trunk	1733	906	1349	690	1.28 (1.20–1.38)	1.31 (1.19–1.45)
Leg and Hip	351	1433	270	869	1.30 (1.11–1.52)	1.65 (1.52–1.79)

likelihood of detection during the warm months, when less clothing is worn and more skin is visible? The two explanations are not mutually exclusive, and it is possible that both have contributed to our observations. Although the relationship of the seasonality of melanoma diagnosis to seasonal variation in attire has not been studied, prior investigations indicate a possibility that the seasonality of melanoma diagnosis represents a biologic process.

Several lines of evidence support the notion that sun light, which peaks in intensity around the summer solstice, June 21, in the northern hemisphere, may have a short-term proliferative effect that could lead to the development of cutaneous malignant melanomas during summertime. In the spring, skin is less effective at screening out U.V. radiation because the seasonal increase in protective pigmentation and thickening of the epidermis has not occurred fully.[15] More intense stimulation of melanocytes by sunlight could occur as a result, leading to their proliferation. Consistent with this hypothesis is the observation by Holman *et al.*[16] that nevi biopsied during the summer are more likely to have a junctional component (suggesting relatively recent development) and an inflammatory response. Similarly, Larsen *et al.*[17] reported an excess of junctional and compound nevi registered at their Centre during the summer half-year (May–October), whereas the total number of nevi showed no such variation. U.V. radiation can also induce immunologic effects in skin that may be important in the development of melanoma.[18,19]

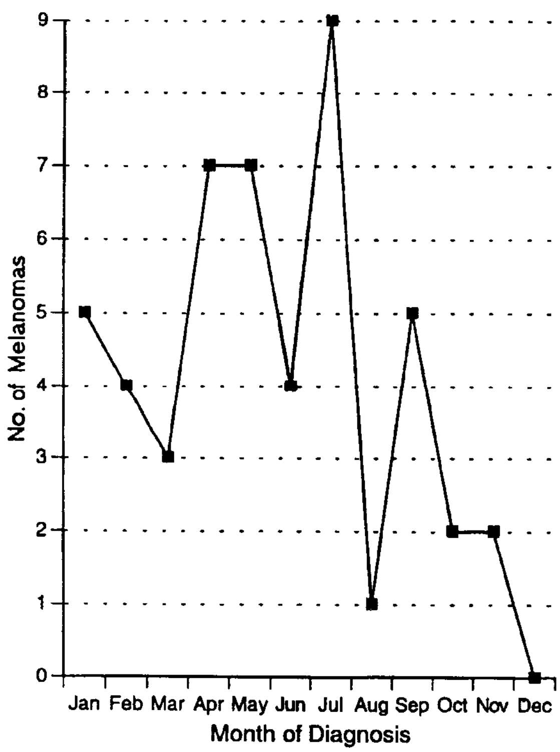

Figure 3. Invasive cutaneous malignant melanoma among melanoma-prone family members by month of diagnosis. Family members are instructed to perform skin self-examinations at least monthly. They also undergo physician-administered skin examinations to to four times a year.

Biological aspects of early melanomas suggest the feasibility of diagnosis shortly after the final stages of carcinogenesis. Unlike internal cancers that are generally detected after they attain the minimum mass detectable by imaging techniques (approximately 1 g), very small cutaneous malignant melanomas can be diagnosed by visual inspection of the skin long before they have a mass of 1 g. Approximately half of melanomas develop from pre-existing naevi, and early melanomas are frequently found because of a change in colour or appearance of a naevus.[20]

The time between the first noticed symptom of cutaneous malignant melanoma and diagnosis can be brief enough to allow detection of a seasonal pattern. In a population-based case–control study, Elwood and Gallagher[21] assessed this duration in 533 patients; they found that 33% of persons diagnosed with cutaneous malignant melanoma were diagnosed within a month of noticing their first symptom, and 50% were diagnosed within 6 weeks. In our data, the lesser seasonality observed for regional stage and distant stage, compared with *in situ* and local stage melanoma, may be to the longer duration between onset and detection for later stages than earlier stages of cancer.

Gender differences in seasonality of diagnosis of melanoma can be attributed to several factors. Koh *et al.*[22] have shown that women are more likely than men not only to discover their own lesions, but also to discover their partner's lesion. The seasonality of melanoma observed among women may therefore provide a closer approximation of their true seasonality of melanoma incidence, and the seasonality of diagnosis of melanoma observed among men may be an underestimate. In addition, greater seasonal differences among women than men in exposure of the skin of the arm and shoulder as well as the leg and hip may contribute to the greater seasonality of melanoma observed among women at those sites. These differences in clothing are probably not as important for the head and neck.

Melanomas of the head and neck occur in skin that is exposed to view throughout the year, and therefore it is unlikely that differential detection explains fully the seasonality observed for this body region. Similarly, seasonal differences in detection are also less likely to be involved in the seasonality of diagnosis of melanoma among pros-pectively followed members of melanoma-prone families, because they are instructed to perform skin self-examination monthly, and are examined by physicians two to four times a year.

A study from Hawaii suggests that the seasonality of diagnosis of cutaneous malignant melanoma is not entirely due to differential detection. Hinds *et al.*[10] reported that in residents of Hawaii, melanoma incidence varies by season in a fashion similar to that of continental USA. We have replicated their main finding in the SEER program data from 1975 to 1990 (not shown). In Hawaii, mean temperatures in August are only 6.5 degrees higher than in January; however, average solar U.V. radiation levels are more than twice as high in August as in January.[23] In such a tropical climate, it is unlikely that the seasonality of melanoma diagnosis is entirely due to the type of seasonal differences in attire that occur in temperate climates.

A hormonal aetiology for the seasonality of diagnosis of cutaneous malignant melanoma has not been investigated. However, seasonal variation has been reported in humans for serum levels of melatonin, 25-hydroxyvitamin D and hormones of the pituitary–gonadal axis.[24,25] Exploration of this area in future research might prove rewarding.

We present here evidence suggesting that the seasonality of diagnosis of cutaneous malignant melanoma is due at least in part to biological processes. This observation may help understand the last stages of carcinogenesis. In addition, our findings suggest that the avoidance of excessive exposure to sun light could be useful in preventing cutaneous malignant melanoma in the short term.

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